## Modeling non-syndromic autism and the impact of TRPC6 disruption in human neurons.

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**Authors:** K Griesi-Oliveira, A Acab, A R Gupta, D Y Sunaga, T Chailangkarn, X Nicol, Y Nunez, M F Walker, J D Murdoch, S J Sanders, T V Fernandez, W Ji, R P Lifton, E Vadasz, A Dietrich, D Pradhan, H Song, G-L Ming, X Gu, G Haddad, M C N Marchetto, N Spitzer, M R Passos-Bueno, M W State, A R Muotri

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**Public Summary:**
While several genetics studies are increasing the list of human genes implicated in autism, few studies can actually throw their impact on human neurons and their relevance to autism. This is the first report of a human stem cell model for sporadic (non-syndromic) autism. Here, we revealed a new gene (TRPC6) implicated in autism pre-disposition. Using multiple models, we showed that TRPC6 is important for neuronal homeostasis. Moreover, the gene is regulated by MeCP2 (the gene mutated in Rett syndrome), revealing common molecular pathways shared by different types of autism. The defects in neurons could be rescued by IGF-1, current in clinical trials for Rett syndrome. Moreover, we were able to test hyperforin, the active principle found in St. John's Wort, to stimulate TRPC6 and rescue neuronal defects in a patient carrying mutation in one copy of the TRPC6 gene.

**Scientific Abstract:**
An increasing number of genetic variants have been implicated in autism spectrum disorders (ASDs), and the functional study of such variants will be critical for the elucidation of autism pathophysiology. Here, we report a de novo balanced translocation disruption of TRPC6, a cation channel, in a non-syndromic autistic individual. Using multiple models, such as dental pulp cells, induced pluripotent stem cell (iPSC)-derived neuronal cells and mouse models, we demonstrate that TRPC6 reduction or haploinsufficiency leads to altered neuronal development, morphology and function. The observed neuronal phenotypes could then be rescued by TRPC6 complementation and by treatment with insulin-like growth factor-1 or hyperforin, a TRPC6-specific agonist, suggesting that ASD individuals with alterations in this pathway may benefit from these drugs. We also demonstrate that methyl CpG binding protein-2 (MeCP2) levels affect TRPC6 expression. Mutations in MeCP2 cause Rett syndrome, revealing common pathways among ASDs. Genetic sequencing of TRPC6 in 1041 ASD individuals and 2872 controls revealed significantly more nonsynonymous mutations in the ASD population, and identified loss-of-function mutations with incomplete penetrance in two patients. Taken together, these findings suggest that TRPC6 is a novel predisposing gene for ASD that may act in a multiple-hit model. This is the first study to use iPSC-derived human neurons to model non-syndromic ASD and illustrate the potential of modeling genetically complex sporadic diseases using such cells.Molecular Psychiatry advance online publication, 11 November 2014; doi:10.1038/mp.2014.141.